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Serum Enzymes†

Variations of Activity in Disease of Muscle

LAURENS P. WHITE, M.D., San Francisco

• In a study of 58 patients with various diseases of muscle or of the neuromuscular system, the serum activity of various enzymes was measured. Abnormal elevation of serum activities of aldolase, lactic dehydrogenase and, to a lesser extent, glutamic-oxalacetic transaminase and phosphohexose isomerase, was an almost constant feature in patients with progressive muscular dystrophy. These elevations were very frequent in dermatomyositis, common in acute cerebral vascular accidents, and rarely seen in other neurological disorders. Abnormal serum activity of iso-citric dehydrogenase was not observed in the course of the present study.

Supplementary protein feeding of patients with muscular dystrophy had no effect on serum enzyme activity, no consistent effect on urinary creatine excretion and no effect on the strength of the patient or the course of the disease.

Dystrophic muscles from a dystrophic strain of mice showed a decrease in activity of lactic dehydrogenase and aldolase below that of control muscle and an increase of iso-citric dehydrogenase activity. These findings, taken with the differences in serum activities of lactic dehydrogenase, aldolase and isocitric dehydrogenase in the dystrophic animals, support the conclusion that dystrophic animals handle these soluble enzymes in quite different ways.

THIS PAPER presents a summary of experience with multiple serum enzyme activity determinations in patients with diseases of nerve and muscle, particularly muscular dystrophy. It has been known for ten years that patients with dystrophy frequently are found to have abnormally elevated serum activity of certain enzymes.* The physiological studies on this abnormality have led to the assumption that the enzyme abnormality was due to an increased permeability of the damaged or diseased muscle membrane to the enzymes contained within the myofibril.[8,20] Similar abnormalities of serum enzyme activities have been found in patients with cancer, myocardial infarction, bodily trauma and a variety of other conditions.[7,24]

Previous studies in this laboratory have shown that in many patients with cancer the serum enzyme activity abnormalities can be reversed by the administration of large amounts of protein.[26] These cancer patients have also been shown to have excessive urinary creatine excretion. The association of elevated serum enzyme activity and creatinuria in these cancer patients is quite similar to that found in patients with muscular dystrophy.[3,14] It was, therefore, of interest to investigate the effect of similar protein feeding upon the serum enzyme activity of patients with muscular dystrophy.

†This is the fifth in a series of articles on serum enzyme activity.

From the Department of Medicine, Stanford University School of Medicine, San Francisco.

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Van Meter[22] and others[29] reported, on the basis of uncontrolled clinical studies in a few patients with dystrophy, that the oral administration of fairly large amounts of protein hydrolysate resulted in uniform clinical improvement. This form of therapy is based on the supposition that dystrophy may be due to inadequate absorption of protein from the bowel or inadequate protein synthesis by dystrophic muscle, an assumption unsupported by experimental observations. Numerous investigators[5,6,23,31] have refuted Van Meter's clinical conclusions. It was, however, pertinent to study, in our patients with muscular dystrophy who were receiving feedings of protein or protein hydrolysates, the effect of such feedings on muscle strength over a period of time, as well as any effects on the objective measurements of urinary creatine excretion and serum enzyme activity.

We have further measured the serum activities of several enzymes in a large group of patients with muscular dystrophy, dermatomyositis and various neuromuscular diseases, as well as in a very large number of patients with diseases not primarily affecting the neuromuscular system. Much of this material has been presented elsewhere.[24,25,27]

MATERIALS AND METHODS

The patients studied were seen at several medical centers. Most of the children with pseudohypertrophic muscular dystrophy were observed at the Muscular Dystrophy Clinic of Children's Hospital, San Francisco. A total of 58 patients with various diseases of muscle or the neuromuscular system contributed blood for these investigations.

The enzyme activities measured have been: aldolase, lactic dehydrogenase (LDH) glutamic-oxalacetic transaminase (SGOT) phosphohexose isomerase, and isocitric dehydrogenase (ICD). The methods for assay have been described previously.[24,25,30] Urinary creatine was measured by the Jaffe method. All patients receiving Amigen® intravenously (pancreatic hydrolysate of casein) or human serum albumin intravenously had serial hematocrit determinations during the period of administration to estimate the extent of hemodilution, and in none was significant change in hematocrit found.

The six patients with muscular dystrophy who were studied during protein feeding were put in hospital, where they were given diets of relatively constant known composition, and daily 24-hour urine collections were started. Blood was taken periodically for enzyme assay and other measurements. After several days of observation, during which careful muscle testing was performed by members of the physical therapy department, protein supplements were begun. One patient was able to take Amigen by mouth, 100 gm. daily. Three received Amigen intravenously in amounts of 50 to 100 gm. daily. Two patients received human serum albumin intravenously. During the period of protein or protein hydrolysate administration, serial determination of serum enzyme activity was continued, as were measurements of urinary creatine. At the end of the experimental period (four to eight days) muscle testing was again done, and was repeated one month later.

Twenty-seven patients with muscular dystrophy were observed over a long period, and blood was

TABLE 1.—*Serum Enzyme Activity in Patients with Pseudohypertrophic Muscular Dystrophy*

Case No.	Aldolase Units/ml.	LDH* Units/0.01 ml.	SGOT* Units/ml.	Hexose Isomerase Units/ml.	ICD* mμM*/ml.	Urinary Creatine mg./24 Hours
1	23.0	217	69	53	.....	.....
2	91.5	218	76	50	144	595
3	23.7	319	54	30	318	.....
4	11.6	170	17	22	.....	.....
5	28.0	270	101	63	126	.....
6	12.1	134	14	19	.....	350
7	10.7	145	18	17	.....	625
8	41.5	338	190	71	228	242
9	24.0	645	110	38	132	.....
10	21.3	211	60	33	.....	136
11	72.0	652	270	91	.....	140
12	15.2	454	.....	18	108	.....
13	46.4	402	.....	84	.....	.....
14	79.0	588	.....	84	208	.....
15	108.0	658	.....	128	288	.....
16	28.2	391	.....	42	.....	.....
17	66.8	.....	.....	.....	.....	.....
18	80.4	.....	.....	.....	.....	.....
Normal	<9.5	<110	<32	<40	<300	

*LDH = Lactic dehydrogenase; SGOT = Glutamic oxalacetic transaminase; ICD = Isocitric dehydrogenase; mμM = millimicromoles.

TABLE 2.—*Serum Enzyme Activity in Patients with Facio-Scapulo-Humeral Dystrophy*

Case No. & Sex	Aldolase Units/ml.	LDH* Units/0.01 ml.	SGOT* Units/ml.	Hexose Isomerase Units/ml.	ICD* mμM*/ml.	Urinary Creatine mg./24 Hours
1 M	11.7	95	35	21	.....	.....
2 M	11.5	86	35	11	.....	.....
3 M	11.2	91	30	25	.....	.....
4 F	10.8	160	....	6	264	453
5 F	6.2	.....	....	40	.....	907
6 M	12.0	.....	....	21	.....	1796
7 M	99.4	.....	....	....	.....	.....
8 F	7.6	.....	....	....	.....	.....
9 F	21.2	.....	....	....	.....	.....
Normal	<9.5	<110	<32	<40	<300	

*LDH = Lactic dehydrogenase; SGOT = Glutamic oxalacetic transaminase; ICD = Isocitric dehydrogenase; mμM = millimicromoles.

TABLE 3.—*Serum Enzyme Activity Before and After Administration of Dietary Supplementation*

Case No.	Age	Dietary Supplement	Duration	Aldolase Units/ml.		LDH* Units/0.01 ml.		Hexose Isomerase Units/ml.		Urinary Creatine mg./24 Hours	
				Initial	Final	Initial	Final	Initial	Final	Initial	Final
1	5	Albumin, 10 gm./day	4 days	40.0	37.7	574	545	59	81	138	.....
2	10	Albumin, 15 gm./day	4 days	21.3	23.6	211	322	33	54	136	.....
3	12	Amigen, 100 gm./day	8 days	35.6	106.8	530	556	32	86	595	339
4	8	Amigen, 100 gm./day	8 days	61.5	46.2	527	511	....	....	242	276
5	16	Amigen, 100 gm./day	8 days	6.3	4.5	121	120	....	....	301	479
6	43	Amigen, 10 gm./day	8 days	9.1	5.8	129	148	....	....	453	584

*LDH = Lactic dehydrogenase.

drawn from time to time for enzyme activity assay. In a few cases, only one assay was done.

Nine patients with dermatomyositis were studied. Two patients were subjected to serial enzyme determinations during the course of treatment with adrenal steroids.

Twenty-two patients with a variety of different neuromuscular disorders were also subjected to serum enzyme assay.

A small group of mice, strain 129, with the genetic pattern dydy, with muscular dystrophy, that were obtained from the Roscoe B. Jackson Laboratory, Bar Harbor, Maine, were studied for the measurement of various enzyme activities in muscle, and the values were compared with those obtained in normal litter-mates with a genetic pattern Dydy. The dystrophic animals were shown to have abnormal activities of various serum enzymes.[16,32]

RESULTS

The values for serum enzyme activities in patients with pseudohypertrophic muscular dystrophy are given in Table 1. From the table it can be seen that no patient had a normal activity of either aldolase or lactic dehydrogenase, whereas normal activities of phosphohexose isomerase and SGOT were seen in about half of the patients. Only one patient had elevated ICD activity. (This patient, a young child, may in fact have had a normal value for a child, since the upper limits of normal in young children have not been definitely determined.)

In the patients listed in Table 1 the range in severity of disease was from mild, with minimal impairment of strength and activity, to most severe, the patients having almost no capacity to care for themselves, decided contracture deformities and being in essentially bed-ridden condition. In many of these patients serial enzyme activity determinations were performed over an 18-month period. There was remarkably little fluctuation of the enzyme levels of most of the patients during this period. Curiously, as the disease progressed, the levels of enzyme activity tended to decrease. The lower values of activity were found either in mild cases, with little impairment of function, or in the most severely crippled, older boys.

Urinary creatine determinations were performed in six of these patients, and the content was abnormally elevated in all.

Seven parents of patients in this group were studied for serum enzyme activities. In none was an abnormal value found for aldolase, LDH, phosphohexose isomerase or SGOT. The mean values were almost exactly the same as the mean values for the normal controls.[7]

Nine patients with the facio-scapulo-humeral form of muscular dystrophy (Déjerine-Landouzy) were subjected to serum enzyme assay, and the results of these determinations are given in Table 2. Normal values for aldolase activity were found in two elderly women. Abnormal LDH activity was found only once, in a middle-aged woman with severe muscle wasting. Abnormal values for SGOT and phosphohexose isomerase were not seen. Three patients had abnormal urinary creatine excretion.

Six patients with dystrophy were studied intensively during the course of dietary protein supplementation. These patients ranged in disability from mild difficulty in climbing stairs to totally bedridden, and in enzyme abnormality from minimum to severe. Table 3 lists the various enzyme activities before and at the termination of the study, together with the duration of treatment and the amount of protein or hydrolysate given. It can be seen that in no patient was the administration of dietary supplements, whether albumin given intravenously, or Amigen given orally or intravenously, followed by significant change in the serum enzyme activity or creatinuria; similarly, in no patient was this treatment associated with any change in muscle strength or function, as measured by objective tests. Two patients reported a transient feeling of increased strength, which could not be verified by increased performance. Chart 1 shows the results of a typical experiment in a young boy with moderately severe disease, who received Amigen intravenously in addition to his regular diet. This child had previously been observed for 13 months as an outpatient, and continuous progression of the disease was noted. The

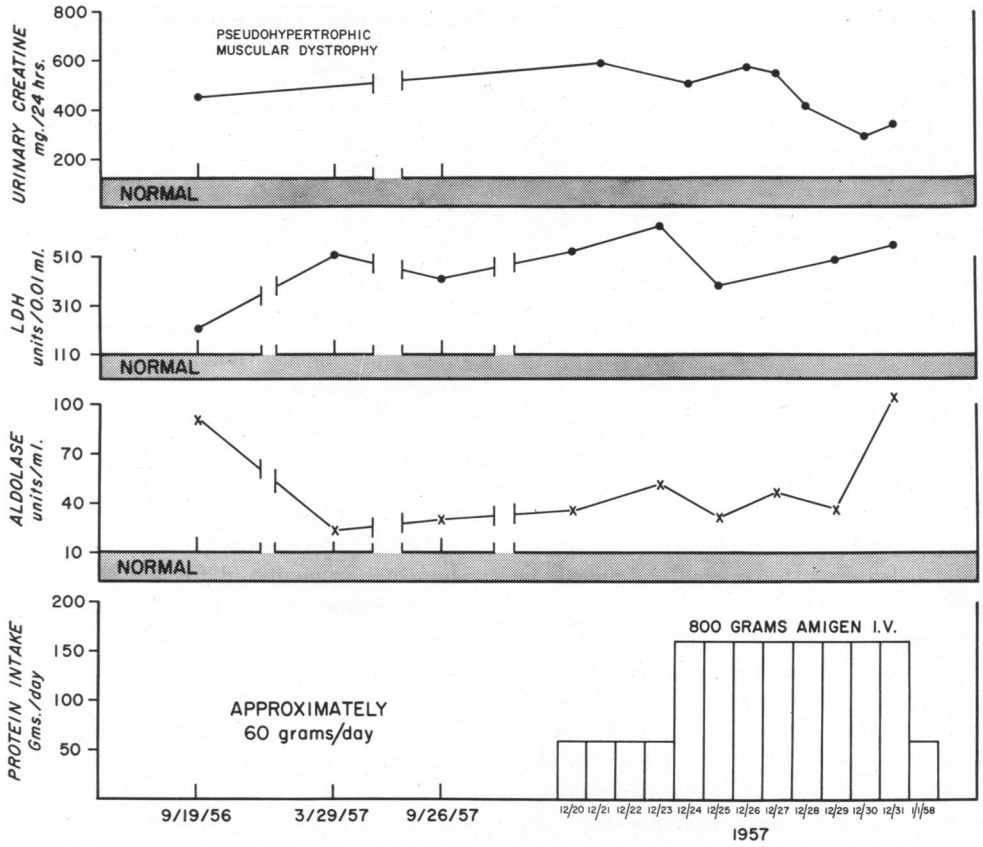

Chart 1.—Serial determinations of serum enzyme activity in a 12-year-old boy with pseudohypertrophic muscular dystrophy. Minimal variation of enzyme activities over a period of one year, and no change during short period of Amigen administration. (LDH = Lactic dehydrogenase.)

TABLE 4.—*Serum Enzyme Activity In Patients with Dermatomyositis*

Case No.	Aldolase Units /ml.	LDH* Units/0.01 ml.	SGOT* Units/ml.	Hexose Isomerase Units/ml.	Urinary Creatine mg./24 Hrs.	Clinical Condition
1	17.2	355	53	44	.....	Moderately severe, generalized
2	4.3	110	9	22	.....	Minimum involvement of arms
3	2.0	116	17	11	.....	Minimum involvement of calves
4	5.3	127	15	42	.....	Mild local involvement
5	24.4	350	80	59	.....	Severe, generalized disease
6	.....	120	....	....	.....	Minor disease of hands
7	126.0	.....	....	....	3220	Most severe, generalized disease
8	14.9	.....	....	....	.....	Moderately severe upper extremity
9	100.0	.....	....	....	.....	Widespread severe involvement

*LDH = Lactic dehydrogenase; SGOT = Glutamic oxalacetic transminase.

Amigen had no effect on his strength or ability to move and play, and no late improvement took place in eight months of observation after Amigen administration. There was no consistent change in the serum activity of any of the enzymes measured.

For comparison, Chart 2, taken from a previously published paper, shows the results of a similar experiment in a patient with cancer who received Amigen intravenously. The dietary supplementation with Amigen was followed by an immediate fall of serum enzyme activities to normal.

Nine patients with dermatomyositis were included in the present study, and serum enzyme activities of each are given in Table 4. These patients had varying degrees of muscle damage, from minimal involvement of interosseus muscles to massive damage to most of the large muscle groups of the body. In general the severity of the disease was well correlated with the degree of abnormality of the serum enzyme activities.

Two of these patients deserve special mention. One, a 43-year-old man (Case 7, Table 4), entered

the hospital with fulminating dermatomyositis involving muscles of the neck, arms, thorax, thighs and calves. He had active gastrointestinal hemorrhage and uremia. His serum aldolase activity was sharply elevated; and in spite of renal damage, he excreted 3220 mg. of creatine in the first 24 hours. When massive doses of hydrocortisone were given intravenously his clinical status improved greatly, serum aldolase values fell to normal in two weeks and creatine disappeared from his urine. He appeared to have full recovery and when last observed two years later was back at work. The second patient, a 45-year-old Japanese-American (Case 5, Table 4), entered with a more indolent although severe form of the disease, with diffuse muscle involvement. Elevated activities of aldolase, LDH, isomerase and SGOT were found; and despite the administration of various hormones, including adrenal steroids and testosterone, the serum enzyme values did not change. Clinically the course was one of unremitting disease. It would appear, therefore, from these two cases, that in dermatomyositis the serum activities of glycolytic enzymes may prove to be an accurate representation of the severity of the disease, and may provide an objective means for judging the early effects of therapy.

Twenty-two patients with various neuromuscular diseases were also studied (Table 5). Three patients with traumatic paraplegia were included. One of them, with acute cord damage, whose status was complicated by peritonitis, had a decidedly abnormal LDH activity. Another, who had disease of longer duration, had an elevated aldolase value. The third patient, in whom the disease was of eight months' duration, had normal activities of each of the enzymes measured. One patient with trichinosis was studied late in the course of disease and was found to have minimum elevation of LDH activity. Patients with myotonia dystrophica, amyotonia congenita, myasthenia gravis, parkinsonism, primary

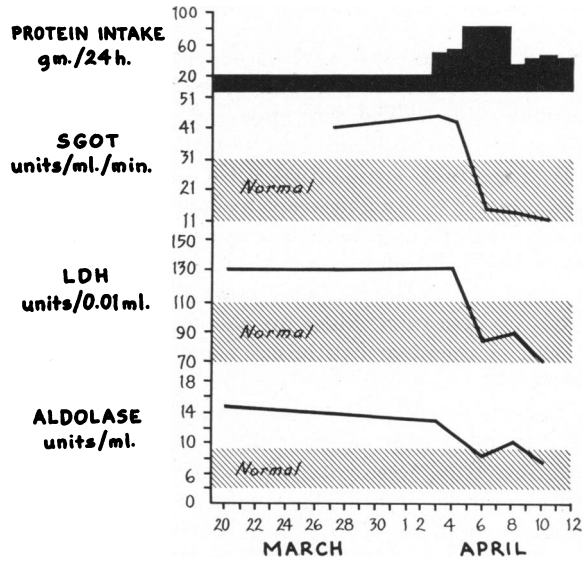

Chart 2.†—Effect of Amigen administration in a patient with cancer who had elevated activity of several serum enzymes. Prompt fall to normal of serum transaminase, lactic dehydrogenase and aldolase after starting Amigen. (SGOT = Glutamic oxalacetic transaminase.)

†Reproduced, by permission, from Ann. N. Y. Acad. Sci. 75:349-356, 1958.

TABLE 5.—*Serum Enzyme Activity in Patients with Various Neuromuscular Diseases*

Case No.	Diagnosis	Aldolase Units/ml.	LDH* Units/0.01 ml.	SGOT* Units/ml.	Hexose Isomerase Units/ml.	ICD* mμM*/ml.
1	Traumatic paraplegia (recent)	28.8	.....	....	....	.....
2	Traumatic paraplegia (old)	7.2	105	26	12	.....
3	Traumatic paraplegia (new)	....	650	....	....	.....
4	Trichinosis	....	128	15	....	.....
5	Myotonia dystrophica	5.0	.....	15	....	.....
6	Myasthenia gravis	7.2	.....	17	....	.....
7	Amyotonia congenita (child)	8.3	186	18	15	.....
8	Primary lateral sclerosis	5.0	86	9	32	.....
9	Parkinsonism	....	93	....	....	.....
10	Cerebellar ataxia (child)	4.2	159	13	20	.....
11	Freiderich's ataxia	7.2	.....	19	....	.....
12	Ataxia (child)	9.1	146	29	20	.....
13	Ataxia (child)	8.9	76	27	10	.....
14	Ataxia (child)	7.0	248	12	30	.....
15	Cerebral vascular thrombosis	7.4	.....	42	....	.....
16	Cerebral vascular thrombosis	5.4	175	80	33	.....
17	Cerebral vascular thrombosis	....	124	....	10	.....
18	Cerebral vascular thrombosis	....	116	....	10	.....
19	Cerebral vascular thrombosis	....	142	....	....	318
20	Cerebral vascular thrombosis	....	161	....	....	204
21	Cerebral vascular thrombosis	....	131	....	....	90
22	Subarachnoid hemorrhage	....	64	....	....	144
Normal		<9.5	<110	<32	<40	<300

*LDH = Lactic dehydrogenase; SGOT = Glutamic oxalacetic transaminase; ICD = Isocitric dehydrogenase; mμM = millimicromoles.

TABLE 6.—*Enzyme Activity Assays in Homogenates of Various Tissues of Dystrophic Mice*

	Aldolase Units/min./mg. Protein 38° C.		LDH* mμM*/min./mg. Protein 38° C.		ICD* mμM*/min./mg. Protein 25° C.	
	Dystrophic	Control	Dystrophic	Control	Dystrophic	Control
Heart	1.4 (1.2-1.6)	1.5 (0.9-1.9)	14.6 (9.6-18.9)	13.9 (10.8-18.3)	105 (86-124)	116 (101-126)
Skeletal muscle	4.4 (4.3-4.5)	6.0 (5.1-6.7)	23.4 (16.0-27.5)	35.8 (26.0-45.5)	13.3 (13.3)	10.9 (3.5-19.2)
Liver	0.8 (0.8)	0.5 (0.5-0.6)	14.8 (5.0-19.2)	13.5 (13.1-13.8)	88 (68-108)	69 (17-108)

*LDH = Lactic dehydrogenase; ICD = Isocitric dehydrogenase; mμM = millicromoles.

lateral sclerosis and various forms of cerebellar ataxia were found to have activities within the normal range. (The few apparently elevated LDH values were in children, in whom LDH activities of this magnitude are normal.) Eight patients with recent cerebral vascular accidents had serum enzyme determinations. LDH activity was abnormal in six of seven and phosphohexose isomerase activity was elevated in the two patients in whom it was measured; no abnormal values for aldolase or SGOT were found. One patient had minor elevation of the ICD activity.

Enzyme determinations on homogenates of tissues of dystrophic mice of strain 129, with genetic constitution dydy, were compared with those of littermate controls, Dydy. These values were also contrasted with those of C57 Black/dba hybrid animals. Lactic dehydrogenase, aldolase and isocitric dehydrogenase activities were measured and expressed in activity per mg. of protein. Table 6 gives the results. Values for aldolase and LDH were lower in dystrophic muscle than in control muscle, while ICD activities were greater in dystrophic muscle than in control. Enzyme values in the heart and liver of dystrophic animals were more nearly those of the control animals. All of the activities were of the same order of magnitude as those in animals of a different strain.[27]

DISCUSSION

The present data confirm many previous observations of abnormal serum activity of certain enzymes in patients with progressive muscular dystrophy and other muscle diseases.* Patients with muscular dystrophy tend to have decidedly abnormal levels of aldolase activity in serum, with decreased aldolase activity in affected muscles. This appears to be true in dystrophic mice as well, both from the work of others[8,16,32] and from the present report. Similarly, serum LDH activity is uniformly abnormal in patients with severe muscular dystrophy; and there is decreased LDH activity in dystrophic muscle of man and mice.[8,16] Less constant are the abnormalities of SGOT and phosphohexose isomerase. A curious fact is that abnormal serum activity of ICD has not been observed in patients with dystrophy, no matter how severe the clinical disease; normal muscle contains a considerable amount of ICD, and it was of great interest that ICD activity in the muscles of dystrophic mice was higher than in controls. It is apparent that dystrophic animals, or their muscles, handle LDH and ICD in quite different manners.

The six patients with active muscular dystrophy who received dietary protein supplementation in the form of Amigen or human serum albumin showed no clinical improvement either during or after such treatment. In none of these patients was there any significant change in serum enzyme activity during protein administration. It has previously been shown that Amigen and albumin do not have a "nonspecific" inhibitory effect on serum enzyme activity.[26] This failure of albumin or Amigen to alter the levels of activity of aldolase, LDH or isomerase in the serum of patients with dystrophy is in contrast to the observation in cancer patients that such protein supplements may frequently produce reversal of abnormal serum enzyme values to normal.[26] It has been suggested that the cause of serum enzyme abnormality in many patients with cancer is muscle wasting due to inadequate nutrition and that the effect of the protein supplements is to provide adequate protein for bodily needs and tumor growth, stopping the muscle wasting which took place to supply these needs. If this explanation is correct in cancer patients, it would appear likely that some other explanation for the serum enzyme abnormality in dystrophy must be sought, for no such reversal of serum enzyme abnormality was produced by protein supplementation. The observations of Zierler[32] and many others are totally in disagreement with any proposition of nutritional origin for dystrophy, such as that proposed by Van Meter.[22]

Our findings of normal serum enzyme activities in parents of patients with muscular dystrophy suggest that there is no genetically transmitted defect of serum enzyme activity. This certainly must mean that the abnormality of serum enzyme activities seen in dystrophic patients is strictly secondary to the primary mechanism of the disease. In numerous other hereditable diseases where enzyme defects have been demonstrated in patients, similar abnormalities have frequently been seen in parents and siblings of affected patients.[10,11,12,13]

*References 1, 2, 4, 7, 9, 15, 17-21, 24, 25, 28.

Our observations on serum enzyme activity in patients with dystrophy followed for long periods without special treatment would indicate that the higher values occur early in the course of the disease, tending to fall as the patient becomes more and more crippled. These observations are similar to those of Schapira and co-workers.[17,18] In cases of roughly the same duration the higher values were generally found in the more severely affected children.

Patients with dermatomyositis showed pronounced variation in serum enzyme activity, the activity being closely correlated with the severity and extent of the disease. In several patients serial measurement of serum enzyme activity proved to be a reliable means of following the effects of treatment, in that patients showing clinical improvement first had a decrease in the serum activity of one or more glycolytic enzymes. In patients not responding to treatment there was no change in serum enzyme activity.

The abnormal activities of serum enzymes in two patients with recent paraplegia presumably reflected the active muscle wasting which was occurring. Similar findings have been seen in acute poliomyelitis.

It was apparent that the rate of tissue breakdown, whether due to wasting disease, infection or some other cause, is of critical significance in the production of elevated serum enzyme activity. The body may be capable of excreting, or inactivating, some excess of these enzymes, but only up to a definite level. When, through more extensive or more rapid tissue damage, amounts in excess of this capacity are poured into the blood, elevated activities result.

The observations on enzyme activities in homogenates of muscle of dystrophic mice, as compared to activities in non-dystrophic litter-mates, were consistent with those reported by Schapira and Dreyfus.[7,8] We, and they, found decreased aldolase and LDH activities in dystrophic muscle, and we noted an apparent increase in ICD in the same muscle. All of these enzymes are freely soluble. Zierler showed that aldolase leaks out of dystrophic muscle at a rate greatly in excess of the rate of leakage from normal muscle.[32] It will be of great interest to learn the rate of leakage of ICD from the same muscle under the same conditions. It is apparent, however, that dystrophic muscle must handle LDH, aldolase and ICD in different ways.

Stanford University School of Medicine, 2398 Sacramento St., San Francisco.

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